Claim 11 was rejected as indefinite because in the Examiner's opinion, it is unclear whether the entire sequence of SEQ. ID. NO. 4 or a fragment of it was being claimed. It is Applicants' position that the claim was clear as written. However, to facilitate prosecution, the claim has been amended.

Claim 11 was also rejected as vague because it was unclear what the term "C9" represented. Applicants have removed this designation from the claim language. Applicants submit that claim 11 is now compliant with 35 U.S.C. § 112, second paragraph.

Claim 6 was rejected as vague and indefinite because in the Examiner's opinion, it is unclear which of the oligonucleotides was being claimed. Applicants submit that it was clear in the claim that "an oligonucleotide sequence" was referring to the double-stranded oligonucleotide. To facilitate prosecution, Applicants have amended the claim. Applicants submit that claim 6 is now compliant with 35 U.S.C. § 112, second paragraph.

The Examiner indicates that claim 23 is rejected under 35 U.S.C. § 112, second paragraph, but fails to detail any rejection of that claim. Applicants respectfully request that this rejection be removed. Appplicants submit that the claims are now compliant with 35 U.S.C. § 112, second paragraph.

Claims 1-5, 7, 15, 18 and 19 have been rejected under 35 U.S.C. § 102(b) as being anticipated by *Davies BR* et al. Applicants respectfully traverse this rejection. The rejected claims are directed to a method of screening and recovering a regulatory DNA. *Davies BR* et al. differ from these claims in that in *Davies BR* et al.(1) the DNA fragments are not tagged by means of a rescue oligonucleotide as defined in the rejected claims and (2) that the recovery of human DNA inserts has not been carried out. The tagging method disclosed in the present application simplifies the insertion and rescue of particularly small fragments that have a low probability to contain repetitive sequences. Withdrawal of the rejection over *Davies BR* et al.is solicited.

Claims 1-5, 18 and 19 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabling. The specification of a patent application is presumptively enabling. *In re Marzocchi*, 157 U.S.P.Q. 504 (CCPA 1968). Here, the entire specification provides a sound scientific basis and description for the claimed subject matter. Neither the claims nor the specification are construction blueprints. They are addressed to one skilled in the art. To support a rejection for non-enablement under 35 U.S.C. § 112, first

paragraph, in view of the well-structured specification and its presumptive enablement, the Office must cite references which show, *inter alia*, that the specific model utilized here does not translate into other models. A mere conclusory statement without a firm scientific basis supported by references does not create a *prima facie* case of non-enablement which forces the Applicants to go forward with rebuttal evidence. Withdrawal of the rejection under 35 U.S.C. § 112 as not enabled is solicited.

At any rate, it is believed that the rewriting of the claims is sufficient to overcome the rejections under 35 U.S.C. § 112, first paragraph.

Claims 17 and 29 were also rejected under 35 U.S.C. § 112, first paragraph, as non-enabling. Applicants respectfully suggest that a *prima facie* case of non-enablement has not been made in this case either.

A medicament is based upon the inactivation or removal of the met DNA. Since the sequence of the met DNA is known, methods based upon the DNA sequence will have the required specificity to target the met DNA. *Scanlon et al.*, (1995): Oligonucleotide-Mediated Modulation of Mammalian Gene Expression. Faseb J. 9, 1288-1296. Inactivation of the met DNA was envisaged to be achieved by using specific DNA designed to form an inactivating triple helix structures with the met DNA. *Tu et. al.* (1995), Inhibition of Gene Expression By Triple Helix Formation In Hepatoma Cells; J of Biol. Chem. 270: 28402-28407, *Wang et. al.*, (1995), Targeted Mutagenesis in Mammalian Cells Mediated By Intracellular Triple helix Formation- a New Approach to Gene Therapy; J. of Cell. Biochem., 385-386. The specific degradation of the met DNA can be achieved by complexing to the triple helix forming DNA an inactivating or DNA degrading chemical or reagent. *Kane et al.* Specific Cleavage of a Triple Helix by Fe-II Center Dot Bleomycin, Biochem. 34: 16715-16724; *Shields et. al.*; Sequence Selective DNA Recognition and Photocleavage- A Comparison of Enantiomors of Rh(En)(2)Phi(3+); Biochem. 34, 15037-15048. These techniques had been widely published before the priority date of the patent as evidenced by the publication dates of the references. Applicant's submit that the claims are in compliance with 35 U.S.C. § 112, first paragraph.

Applicants have made a genuine effort to respond to the Examiner's objections and rejections in advancing the prosecution of this case. Applicants believe all formal and

substantive requirements for patentability have been met and that this case is in condition for allowance, which action is respectfully requested.

The Examiner is requested to telephone the undersigned to discuss resolution of any issues necessary to place this case in condition for allowance.

A check in the amount of $890.00 is enclosed to cover the three-month Extension Of Time Petition fee. Please charge any additional fees or credit any overpayments as a result of the filing of this paper to our Deposit Account No. 02-3978 — a duplicate of this paper is enclosed for that purpose.

Respectfully submitted,

PHILIP S. RUDLAND ET AL.

By _____
THOMAS W. CUNNINGHAM
Reg. No. P48,722
Attorney/Agent for Applicants

Date: ***September 17, 2001***

BROOKS & KUSHMAN P.C.
1000 Town Center, 22nd Floor
Southfield, MI 48075
Phone: 248-358-4400
Fax: 248-358-3351

Attachment

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In The Specification

On page 5, please replace the paragraph at the bottom of the page beginning "To aid the rescue of metastasis-inducing human" with the following paragraph:

To aid the rescue of metastasis-inducing human DNA sequences from the rat transformant cell lines, all the HindIII-fragmented DNA's from one such metastatic transformant, R37-Ca2-LT1 (Table 1) were tagged at both ends with double-stranded synthetic oligonucleotides that provide restriction enzyme and unique PCR primer sites. (SEQ. ID. Nos: 7 and 8.) These are shown in Fig. 1 The tagged DNA fragments include 4 restriction sites: *Sfi*I and *Not*I, a defective *Hind*III site at the 3' end for linking to the *Hind*III sites at the ends of the human DNA fragments, thereby destroying it, and an internal *Hind*III site located near to the 5' end, which when cut after ligation generated new fragments with *Hind*III ends. The fragments were transfected into the parental Rama 37 cells, and after transfer of the cells to the mammary glands of syngeneic rats, metastatic cell lines were isolated from the resultant rat lung metastases. The tagged, fragmented DNA incorporated into the metastatic transfacted Rama 37 cell lines was directly amplified between the tags by PCR and yielded bands at about 1300 to 1500 bp that were responsible for the metastasizing ability of the transfected cells. These results are shown in Fig. 2 which shows the DNA fragments produced by PCR of metastatic transformants. Two new cell lines, established from the culture of lung metastases of R37-Ca2-HT (tagged, metastatic DNA transformant) and R37-Ca2-H (untagged, metastatic DNA transformant) (see Table 1) in rats were termed HTLu and Hlu, respectively. They were run against the tagged benign transformant cell line R37-B-HT and the tagged metastatic transformant R37-Ca2HT. Cellular DNA was amplified by PCR using a short oligonucleotide primer of 22 bp from positions 3-24 of the tag sequence as shown in Fig. 1. Compared with the control DNA's from Hlu and B-HT cells, two extra bands, F1 and F2, of about 1300 bp and 1500 bp respectively, were specifically amplified from genomic DNA of the Ca2-HT and HTLu cells when PCRed DNA samples were run on 0.8% agarose gels containing ethidium bromide and photographed in U.V. light. The fluorescent bands of DNA are shown in negative imaging for clarity. Cloning of these pooled DNA's yielded six independent

fragments and the results are illustrated in Fig. 3. Fig. 3 shows pBluescript clones of etastatic DNA fragments F1 plus F2. The two broad PCR DNA fragments F1 and F2 were excised from the gel in Fig. 2, combined, and cloned directly using the AT procedure into a suitably modified pBluescript vector and the clones of recombinant vectors were cut with *Hind*III to excise the cloned fragments. These cut recombinant vectors were analysed on a 0.8% agarose gel containing ethidium bromide and photographed in U.V. light. The sequences of some clones eg. C10 and C9-DNA's were identical; the six independent sequences arose from clones numbered C2, C5, C6, C9, C12 and C20 and hence are referred to as C2-DNA, C5-DNA etc as shown in Fig. 3. The position of the vector (Vec) DNA and insert (Ins) DNA are indicated and a standard molecular weight ladder in kilobase pairs (kbp) is shown in lane M. Transfection of these cloned DNA fragments singly into the parental benign cell line confirmed that all fragments (C2, C5, C6, C9, C12 and C20-DNA's) produce metastases. These are shown in Table 2 which tabulates the incidence of tumours and metastases for Rama 37 cells transfected with cloned Met-DNA's. The superscript a - e indicate:—

On page 9, please replace the paragraph at the bottom of the page beginning "Surprisingly, the sequences of these Met-DNA's" with the following paragraph:

—Surprisingly, the sequences of these Met-DNA's ([sequence 1 to 6 hereafter] hereafter SEQ. ID. Nos.: 1-6), although human in origin, do not correspond to known genes and most do not include any known open reading frames. Furthermore none of these Met-DNA's are expressed as mRNAs in their transformants and hence are not dominantly-acting oncogenes. They therefore contain entirely novel short stretches of regulatory DNA capable of inducing metastasis.

On page 12, please replace the paragraph at the bottom of the page beginning "According to a third aspect of the present" with the following paragraph:

According to a third aspect of the present invention there are provided DNA consisting essentially of a regulatory DNA capable of inducing metastasis from [sequence 1] SEQ. ID. NO. 1:

On page 13, please replace the paragraph in the middle of the page beginning "According to a fourth aspect of the present" with the following paragraph:

According to a fourth aspect of the present invention there are provided DNA consisting essentially of a regulatory DNA capable of inducing metastasis from [sequence] SEQ. ID. No. 2:

On page 14, please replace the paragraph at the top of the page beginning "According to a fifth aspect of the present" with the following paragraph:

According to a fifth aspect of the present invention there are provided DNA consisting essentially of a regulatory DNA capable of inducing metastasis from [sequence] SEQ. ID. NO. 3:

On page 14, please replace the paragraph in the middle of the page beginning "According to a sixth aspect of the present" with the following paragraph:

According to a sixth aspect of the present invention there are provided DNA consisting essentially of a regulatory DNA capabel of inducing metastasis from [sequence] SEQ. ID. NO. 4:

On page 15, please replace the paragraph at the top of the page beginning "According to a seventh aspect of the present" with the following paragraph:

According to a seventh aspect of the present invention there are provided DNA consisting essentially of a regulatory DNA capable of inducing metastasis from [sequence] SEQ. ID. NO. 5:

On page 16, please replace the paragraph at the top of the page beginning "According to a eighth aspect of the present" with the following paragraph:

According to [a] an eighth aspect of the present invention there are provided DNA consisting essentially of a regulatory DNA capable of inducing metastasis from [sequence] SEQ. ID. NO. 6:

1 (Amended) A method of screening and recovering a regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis comprising the steps of:

i. transferring [tagged] fragments of [a] human DNA of less than 1.5 kb in length from malignant, metastatic cancer cells which have been tagged at both ends with double-stranded synthetic oligonucleotides that provide restriction enzyme and unique primer cites into a cell line that produces only benign, non-metastasizing tumours when injected into a syngeneic animal;

ii. injecting the transformed cells into the syngeneic animal;

iii. selecting those animals in which metastasizing tumours have been identified; and

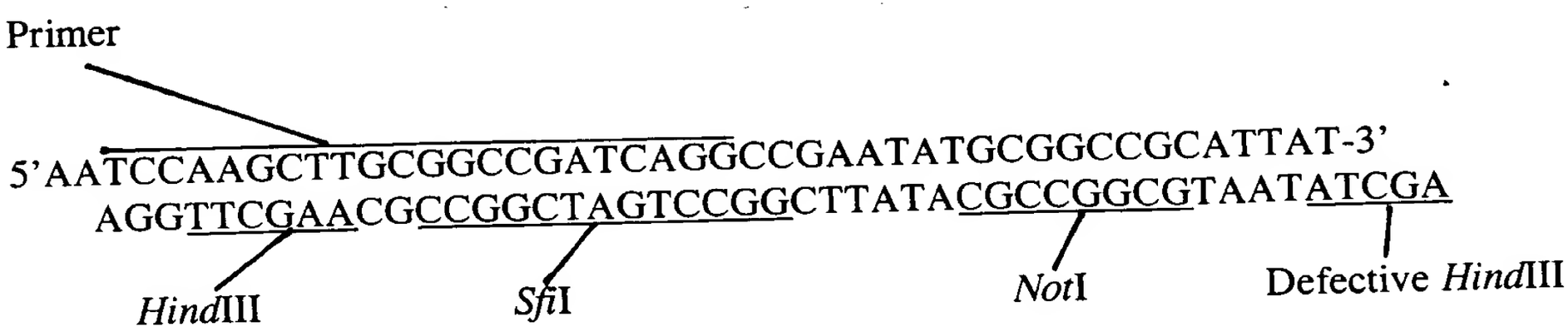
iv. recovering the regulatory DNA capable of inducing metastasis therefrom.

2. (Amended) [A] The method [as claimed in] of claim 1 [in which the] wherein said fragments of human DNA are between 1.3 and 1.5 kb [transferred in step 1 are from 0.1 to 50 kilo base pairs] in length.

Please cancel claim 3.

4. (Twice Amended) [A] The method as in claim 1, in which the cell line that produces only benign non-metastasizing tumours is a rat mammary epithelial cell line.

6. (Amended) [A] The method [as claimed in] of claim 5 wherein the [tag is an] double-stranded synthetic oligonucleotide tag has the following oligonucleotide sequence:



Attachment

7. (Amended) A regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis consisting essentially of a human DNA fragment of less than 1.5 [kilobase pair] kb in length and comprising a sequence selected from the group consisting of SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3, SEQ. ID. NO. 4, SEQ. ID. NO. 5, and SEQ. ID. NO. 6, obtained from a malignant, metastasis cancer cell.

11. (Amended) DNA consisting essentially of a regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis and has the sequence of SEQ. ID. NO. 4 [from sequence 4].

[C9]

[AGTTGGGGAC ACAGCTTGCT TGATTAAGAT GTTTCTTGGG AAAAGGAGTT
AAGCCTAATG ATTTCCAATG GAAAGGACTG CTAATTGGGG AGGCAATGTT
GCTTAATTGG GACACCTGCG GGTAATTAAA AGCTCTCTCC CAGTGGCCTT
TCCTGTTTTT GGCTCTGGGA GGCGAAGGCA TTGAGAGGGA TGCAGGCATT
CTAAGGGCTG GTTCTTGGTT TCTCCCTTCC CCTCTGTCCA AACTCAGTGA
GGTATCCCTG TCTGTGCTGT CCTTAGAGTG CCGTCCTGAG GCCTTGGTGA
GTTAAGGTCT CTGGATCTGA GCTGCCTCAG GGAAACGCAT GAGCTCATTG
GAAAGGGGAG AACCAGGCAA AGGTGTTGGC TGTGACCTCA GAATTCTGAG
GGGCAAAGGT TCAAGGCTAA CTCTCATTAT AGAGCAAGTT TGAGACTGGC
CTGGGAACAA AAATATAAAG TGAGTGAGGT CATATGACAG CACCTGAGGA
GTCCTGTCCC TAGAGATCAT AAGGACCTGG CTGCTGGGGA CTTGTTGCAG
ATGGCACTTT GTGTCGAGAG AGGGGACCTG CCCCAGCATG GGAGGCCCTG
GAAGATCCTC TGGATTAACT GTGAACACTG ATTGCTGCTT TATACCTGGA
GTTGTGCTGT TATCTGGTAC ACATCTGCTG GGTGAATGAG TTCATGGGCT
TTATTTCAGT GAGGTATTTA CCTGAGGAGA AAGAAGGACT GGTGCCACAA
AGCACAGCTT TTAAATCTGT GGGTTGTGAC CCATTATGGA CTATCATAAC
TGAGTGCAGG TATCAAGAAT ACTTTAGCAG GTGGTAAAAA GATTTTTGAA
TGCGCAACGA CCAAAACTGA ACTCAAAAAT CAAGCATGGC ATGGATCCTG
GGTGCTCCTG GAAGCACTTG CCTTTACTGC ATTGTGCGAC TTGACGGTAG
CCTTGGTTCT GAATGCACAA CACGTGGGCT TTGGGCTGCA CAGGCCACCA
CGCCGTGCCT GAAACACCTC AGCTCAGGTT TGTGGCTATG TCCTATGACT
TGGACTTACT TTTATTGCAC ATATAAATAT]

15. (Amended) A probe specific to a regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis as claimed in claim 7 [any of claims 7 to 13].

16. (Amended) A kit for diagnosing the likelihood of a cancer metastasizing comprising a probe of claim 13 [as claimed in claim 15] and one or more of a color [colour] indicator, an oligonucleotide primer, materials for gel analysis and materials for DNA transfer or hydridisation.

17. (Amended) A medicament adapted to target a regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis as claimed in claim 7 [any of claims 7 to 13].

23. (Amended) A probe specific to a regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis as claimed in claim 11.

29. (Amended) A medicament adapted to target a regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis as claimed in claim 11.